* NOTICES *

TECHNICAL FIELD

(Field of invention)
Generally this invention relates to a field of a drug delivery system based on a liposome.
[0002]
(Explanation of a background art)
A curative effect of a substance prescribed for the patient usually relates to quantity and speed to which the substance reaches a blood flow directly. Many factors which have on capability for the substance to reach general circulation exist. Control and maintenance in physicochemical characteristics and a suitable absorption part of versatility of a design of a formula of an intrusion site to the body, a physical form of the substance, and a product, its compound, and an excipient of localization of the substance are included in these.
[0003]
Although oral delivery of a therapeutic substance is the most general form of delivery for convenience merit of administration, and simplicity today, it is not the most reliable route of administration, but is inefficient-like often, and is unstable and is obtained. A factor which affects capability for absorption of a substance administered orally, therefore its substance to reach a blood flow relates to change of a physiological factor in the physicochemical characteristics of the substance, and a gastrointestinal tract, and a medication form. The conventional oral medication form consists of a solution, suspension, powder, 2 partial gelatine capsule, a soft gelatine capsule, a compressed tablet, and a coated tablet. Gastrointestinal tract absorption is the quickest with a solution, and it is common to become late gradually as it faces to a coated tablet in turn enumerated upwards. Generally, since the dissolution is not a rate determining step in an absorption process, a lipid medication form is absorbed earlier than a solid form.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
(The background of invention)
(Field of invention)
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[0002]
(Explanation of a background art)
The curative effect of the substance prescribed for the patient usually relates to the quantity and speed to which the substance reaches a blood flow directly. Many factors which have on the capability for the substance to reach general circulation exist. Control and maintenance in the physicochemical characteristics and the suitable absorption part of the versatility of the design of a formula of the intrusion site to the body, the physical form of the substance, and a product, its compound, and an excipient of the localization of the substance are included in these.
[0003]
Although oral delivery of a therapeutic substance is the most general form of the delivery for the convenience merit of administration, and simplicity today, it is not the most reliable route of administration, but is inefficient-like often, and is unstable and is obtained. The factor which affects the capability for absorption of the substance administered orally, therefore its substance to reach a blood flow relates to change of the physiological factor in the physicochemical characteristics of the substance, and a gastrointestinal tract, and a medication form. The conventional oral medication form consists of a solution, suspension, powder, 2 partial gelatine capsule, a soft gelatine capsule, a compressed tablet, and a coated tablet. Gastrointestinal tract absorption is the quickest with a solution, and it is common to become late gradually as it faces to a coated tablet in the turn enumerated upwards.

Generally, since the dissolution is not a rate determining step in an absorption process, a lipid medication form is absorbed earlier than a solid form.

[0004]

It was a long ideal target of drug delivery technology to design the medication form which makes the maximum the safety of the compound which optimizes validity, and makes drug reliability the maximum, and is sent. An oral medication form began to come to be optimized in the second half of the 1940s and the first stage of the 1950s when gradual release technology appeared in the medicine manufacture field. The theoretic advantage of this new type of delivery system was improving drug performance by increasing the temporal duration of an operation of a drug and decreasing the number of times of medication (dosing interval) needed in order to attain a curative effect. The control drug delivery technology which was a new concept of making the effect of a drug improving was developed late in the 1960s. The theoretic advantage of this technology controls the speed of the dissolution from a solid medication form, reinforces bioavailability, improves safety, and is decreasing the number of times of medication. In the past 20 years, the new concept in oral medicine thing delivery technology was developed, and it is called the therapy system. The important element of a therapy system is taking in the advanced operation control which answers a stimulus and emits a drug to suitable time from a medication form (for example, wax matrix by which the preliminary program was carried out).

[0005]

A capsule is a target conventionally which is used all over the world about a drug, a vitamin, and a nutrition supplement thing, and is a medication form of a common solid. a drug substance is enclosed in the gelatin wall (the husks in which this of two portions is hard -- or it is either of the soft husks (known also as a soft elastic capsule)) of a capsule. The soft elastic capsule (SEC) is soft spherical gelatin husks.

It is partly thicker than the husks of a hard gelatine capsule.

Gelatin is plasticized by addition of glycerin, sorbitol, or a similar polyol. The greatest advantage of the soft gel capsule to 2 partial gelatine capsule is being able to encapsulate lipid, half-lipid, and a paste for the manufacturing process to which soft gel doubles and carries out the sealing seal of every [two one side]. Some manufacturing processes by which a soft gel capsule is produced exist, and a plate process, a rotary metallic mold (rotary die) process, a Norton capsule machine and Accogel, or a Stern machine is contained in these. When the substance encapsulated by newer technology carrying out the seal of the upper part and the lower part together bars a break through, 2 partial gelatine capsule makes it possible to permit lipid, half-lipid, and a paste.

[0006]

Liposomes are microscopic three-dimensional lipid particles.

The aquosity division was surrounded and it is made of a phospholipid double layer membrane to separate.

It is thought that discovery of the liposome was made by Alec Bangham (first British biologist and internist to indicate the lipid particles which swelled in early the 1960s) (Bangham A. et al., J.Mol Biol., 13, 238, 1965). However, the proof of observation of a multiplex layer liposome exists tracing back to 1911 (Lasic, D., Liposomes, 1993). 20 years after Bangham and its associate indicated their discovery, the field of liposome science begins to be established and pharmacological and pharmacologic rationality which justifies using a liposome as a drug carrier came to be carried out. Now, it goes over medical application of a liposome extensively from a systemic anticancer therapy to enhancement of local anesthesia and gene delivery.

[0007]

Taking-orally use of a liposome starts first in the mid-1970s. Contribution (for example, fully systematized structure which can encapsulate various compounds with a good safety profile) of the liposome based on phospholipid was well-known those days. Medical-studies persons thought that this was ideal application which reinforces gastrointestinal tract absorption potentially, protects the ingredient encapsulated from metabolic decomposition, and emits the thing probably encapsulated slowly, then provides a gradual release form. Early research showed that the drug encapsulated by the liposome was absorbed better than the drug (or "isolation") which is not encapsulated by the liposome. In addition to the drug molecule, oral delivery of protein, peptide, and the enzyme was carried out by the liposome. In the trial in which the oral treatment using the blood coagulation factor XIII for a hemophilia is developed, The new technology which enables high yield prehension of the factor VIII to the inside of a liposome was developed (Gregoridias, G. et al., J.Microencap., I(1):33-45-1984). The factor VIII encapsulated by the liposome was administered orally to the patient, and was absorbed from the stomach and intestines (Sakuragawa N., Thrombosis Research 38(6):681-5-1985). Although the passion in early stages of the insulin encapsulated by the liposome was little, it was shown that a significant quantity of the insulin might reach circulation (Woodly, JF, and Critical Rev Ther.Drug Carrier Sys.2(1):1-18-1985). The significant antibody response was induced after internal use of liposome prehension snake venom (an enzyme and peptide) as compared with there having been no response from the poison of isolation (New, RR, Toxicon, 23(2):215-9-1985).

[0008]

The possibility for therapeutic use of the versatility of an oral liposome is proved more by these days. the superoxide dismutase (powerful anti-oxidant used in the treatment of a radiation induction type fibrosing disease) (Regnault C. et al..) encapsulated by the liposome The increase in the bioavailability of Biopharm &Drug Disp 17,164-174-1996 (this is not well absorbed in taking orally) was 57% in the liposome of 14% (isolation) to ceramide. The

hypocalcemia was observed in after-administration 1 hour of the liposome filled up with 1 mg of calcitonin (Arien A. et al., Pharm Research 12(9):1289-1292-1995). This result should be surprised. Although the liposome was considered to be unstable to the operation of bile salt, it is because they protected peptide from zymolysis selectively. In another research, the recombination human erythropoietin (Epo) used in order to deal with kidney ischemia (renal anemia) was encapsulated in the liposome. The bioavailability of the taking orally Epo was poor. It is protein and is because it is decomposed by protease within GI pipe. Absorption, a long-term pharmacologic effect, and a lug are observed, this is caught by the part which is before a liposome invades into a blood flow, and it suggests inducing a releasing effect (Maitani Y., J Pharm Sc 85(4):440-445-1996).

[0009]

The problems relevant to the pharmaceutical sciences which accompany administering a liposome orally are pH of the 1 stomach, 2 bile salt, and three digestive enzyme (mainly lipase). pH by which the stomach is not buffered is crossed to the range of 1.5-2.5, and can cause the chemical instability of a liposome membrane surface.

[0010]

Bile salt acts as a surface-active agent, and causes the instability of a liposome double layer by emulsification. In the case of exposure to lipase and other enzymes, the polar head group of phospholipid or the acyl chain of phospholipid is cut, therefore liposome particles may be burst.

[0011]

(Explanation of invention)

In order that specific chemical change and change of stearic acid may help stability, do to a liposome, but the inclusion of the fluid liposome dispersed matter to the capsule of a gelatin base can improve stability, and can provide a convenient dosage form, and can assist the sustained-release characteristic of a liposome. This invention relates to the new delivery system for an activity substance extensively biologically, and biologically, an activity substance is encapsulated by this into a liposome, or is prescribed as a pre liposome formula thing, and, subsequently is put in to a capsule. This capsule may be 2 partial capsules in which preliminary formation is carried out and the ** gel capsule which can permit a specific quantity of water, 2 partial capsules which can permit a specific quantity of water, or a liposome is subsequently dried. Although the activity biologically substances in this invention may be a drug, a nutrition supplement agent, a vitamin, a mineral, an enzyme, hormone protein, and polypeptide, they are not limited to these.

[0012]

An activity biologically substance with a delivery system of this invention deficient in the suitable :1 oral solubility especially for the following. (For example, morphine, aciclovir,

propanol, fluoxetine), Whether it is absorbed from a gastrointestinal tract 2) Or the drug which is hardly absorbed and which was discovered newly, It must have been absorbed from protein, peptide, and 3GI pipe, And the drug, protein, hormone, and nutriment (for example, vitamin B_{12}, calcitonin, an insulin, erythropoietin, superoxide dismutase) which must be prescribed for the patient according to an invasiveness course (for example, pouring or pernasal inhalation).

[0013]

In addition to being incorporated by an oral route, the liposome capsule unit containing the substance encapsulated biologically is used by local use unit (unit-of-use) application, or may be used in other application courses like [in an eye, a nose, the rectum, or a vagina].

[0014]

The liposome of this invention consists of arbitrary double stratification lipid, and phospholipid, sphingolipid, sphingoglycolipid, and ceramide are mentioned to this. The typical size ranges of these liposomes are 20 nm - 1000 nm. It rehydrates, or is dried, or these liposomes are hydrated selectively, or may be hydrated by completeness. The thing which was done for liposome encapsulation and which use a pre liposome formula thing as an activity substance (liposome drug conjugate) biologically is also possible. This formula thing consists of an activity substance, phospholipid, and cholesterol biologically, and forms a liposome in the case of contact with water. A liposome may be dynamically stabilized by the optimal mole ratio of 2:1 using specific phospholipid (for example, phospho RIPON (phospholipon) 90H) and cholesterol. It is expected that the optimal mole ratio changes with specific selected phospholipid. This stability can protect a liposome from GI decomposition.

[0015]

A gelatine capsule has the lower admissibility to water in the inside and exterior. The usual water admissibility to a ** gel capsule is 10% inside. The concentration of the water in a liposome formula thing may be the range of 60 to 90% of water. The fundamental constituent of this invention is a formula thing of the liposome which has comparatively a small amount of water (5 to 10% of range). By producing a liposome in a low-water-flow nature system, this liposome can encapsulate an activity substance biologically, and restricts exposure of the water to internal lining of a capsule. The concentration of water should not exceed the concentration of the admissibility of the capsule meant. The capsule desirable to this invention can permit water in 15 to 20% of range.

[0016]

The encapsulation to the gelatin husks of a liposome improves the stability of a liposome. It is because it is protected from exposure to air and is so protected from oxidation. This increases the shelf-life of a product. Encapsulation defends a liposome drugs complex also from disassembly of the liposome by the emulsification and the slaking property enzyme of pH with the low stomach, and bile salt origin, and a drug substance at first. This defense may be

further reinforced, when the film of the coat of a capsule is carried out by hydroxyethyl methyl cellulose propylethyl acetate or polymer like hydroxypropylmethylcellulose propylethyl TARETO (thallate).

[0017]

Conventionally, all the administration of the oral liposome was given by the gavage syringe behind the throat by intubation to the direct small intestine as a liquid, or has been given by direct dropping to a mouth. These are the medication methods of a dramatically unreal treating agent. It is because these are troublesome, are obtained, and provide an inaccurate dosage and cannot deal with it easily for a patient. It has an unpleasant taste (it is severe and hard to intercept) bitter [an activity ingredient] and astringent biologically [a large number]. The liposome in a capsule medication form is simple, the unit use which is easy to manage is provided, and this tends to be more easily dealt with by the patient than the liposome product of the usual liquid form. The medication form (for example, capsule) which is easy to take in draws the increase in the compliance by a patient. Non compliance is an everyday occurrence at a troublesome thing. The thing exceeding the half of the prescription of 1,600 million written in the U.S. every year was adopted incorrectly, and it has gone wrong that 30 to 50% of the medication by which a prescription was written draws the intended result. The economical result of the non compliance of medication is over 100 billion yen every year. The significant barrier to compliance is a complicated resume. Use of a simple medication formula thing is mentioned to reduction of the complexity of a resume. It has estimated, if you do not like that 50% of Americans' groups take in an oral liquid. A specific compliance problem is conquered by supplying a liposome in a capsule. Most of the argument and development of an oral medication form for a liposome is not made till today, and there is no oral liposome medication form of available marketing.

[0018]

The gel cap used the best in this invention is changed in size and form. Although an elliptic type, a prolate ellipsoid type, cylindrical, a round shape, and a torpedo type are mentioned to various form, it is not restricted to these. The size of the soft capsule of elasticity is measured by the quantity of the liquid which may be stored into a capsule. The size ranges of the ** gel capsule of this invention are 0.045 cc (0.75 minim) - 5 cc (81.2 minims). ; whose typical size ranges of 2 partial capsules are 600 mg - 30 mg -- the capsule of these -- 000 (maximum)-5 (minimum) -- ******** with a number.

[0019]

(EXAMPLE)

(Working example 1)

[0020]

[Table 1]

ビタミンB_{12}ＬｉｐｏＣａｐ処方物	
成分	濃度（％）
精製水，ＵＳＰ	１０
シアノコバラミン，ＵＳＰ	０．３４５
ホスホリポン　９０Ｈ（ＤＰＰＣ）	3
コレステロール，ＮＰ	2
ビタミンＥ，ＵＳＰ	1
ベンジルアルコール，ＮＦ	1
プロピレングリコール，ＵＳＰ	８２．６５５

An ingredient is mixed and a liposome is produced using an injection method (Lasic, D., Liposomes, Elsevier, 88-90-1993). The liposome mixture was cooled, and 0.7 ml was drawn in a 1-ml insulin syringe, and it poured in to the opening terminal of the ** gelatine capsule, and, subsequently the seal was carried out with tweezers. The obtained capsule contains vitamin B_{12} of 2500mcg. The manufacturing method (for example, rotor Riidai process (rotary die process)) in the large scale of the restoration gel cap is a method desirable to commercial application.

[0021]

(Working example 2)

[0022]

[Table 2]

補酵素Q_{10}ＬｉｐｏＣａｐ処方物	
成分	濃度
精製水，ＵＳＰ	5
ホスホリポン　９０Ｈ（ＤＰＰＣ）	5
コレステロール，ＮＦ	3
ビタミンＥ，ＵＳＰ	1
CoQ_{10}	１．２９
ソルビン酸カリウム，ＮＦ	1
プロピレングリコール，ＵＳＰ	８４．４６

An ingredient is mixed and a liposome is produced using an injection method (Lasic, D., Liposomes, Elsevier, 88-90-1993). The liposome mixture was cooled, and 0.7 ml was drawn in

a 1-ml insulin syringe, and it poured in to the opening terminal of the ** gelatine capsule, and, subsequently the seal was carried out with tweezers. The obtained capsule contains CoQ10 [10-mg]. Restoration of the gel cap in a large scale is best to use other things like the rotor Riidai method or a Norton capsule machine.

[0023]

(Working example 3)

[0024]

[Table 3]

ビタミンE　LipoCap処方物	
成分	濃度（%）
オレイン酸ソルビタン	2．0
ビタミンE，USP	89．8
精製水	4．0
ソルビン酸カリウム	0．2
ポリソルベート20	2．0
ホスホリポン90（DPPC）	2．0

An ingredient is mixed and a liposome is produced using an injection method (Lasic, D., Liposomes, Elsevier, 88-90-1993). The liposome mixture was cooled, and 0.7 ml was drawn in a 1-ml insulin syringe, and it poured in to the opening terminal of the ** gelatine capsule, and, subsequently the seal was carried out with tweezers. The obtained 1-g capsule contains the vitamin E of 898IU. The filling method (for example, the rotor Riidai method) in the large scale for restoration of the gel cap is a desirable method for commercial application.

[0025]

(Working example 4)

[0026]

[Table 4]

L－カルニチン　LipoCap処方物	
成分	濃度
プロピレングリコール	3．0
Lycosin－75^{R}（Roquette）	73．5
L－カルニチン	20．0
ホスホリポン80H（DPPC）	3．5

An ingredient is mixed and a liposome is produced using an injection method (Lasic, D., Liposomes, Elsevier, 88-90-1993). The liposome mixture was cooled, and 0.7 ml was drawn in a 1-ml insulin syringe, and it poured in to the opening terminal of the ** gelatine capsule, and, subsequently the seal was carried out with tweezers. The obtained 1-g capsule contains 735 mg of L-carnitine. Restoration of the gel cap in a large scale is best to use other things like the rotor Riidai method or a Norton capsule machine.

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CLAIMS

[Claim(s)]
[Claim 1]A liposome capsule medication unit containing a liposome containing a biological active substance enclosed in a capsule.
[Claim 2]The liposome capsule medication unit according to claim 1 which comprises arbitrary double stratification lipid in which said liposome contains phospholipid, sphingolipid, sphingoglycolipid, and ceramide.
[Claim 3]The liposome capsule medication unit according to claim 1 chosen from a group which said biological active substance becomes from a drug, a nutrition supplement agent, a vitamin, a mineral, an enzyme, hormone, protein, and peptide.
[Claim 4]The liposome capsule medication unit according to claim 1 prepared by incorporating a pre liposome formula thing containing said biological active substance, or a biological active substance enclosed in a liposome into said capsule.
[Claim 5]The liposome capsule medication unit according to claim 1 in which said biological active substance is CoQ_{10}.
[Claim 6]The liposome capsule medication unit according to claim 1 in which said biological active substance is vitamin B_{12}.
[Claim 7]The liposome capsule medication unit according to claim 1 in which said biological active substance is vitamin E.
[Claim 8]The liposome capsule medication unit according to claim 1 in which said biological active substance is L-carnitine.
[Claim 9]The liposome capsule medication unit according to claim 1 in which said capsule is a soft gel capsule.
[Claim 10]The liposome capsule medication unit according to claim 9 in which said capsule is water tolerance [Claim 11]The liposome capsule medication unit according to claim 10 which said water tolerance capsule becomes from two portions.

[Claim 12]How to be the method of prescribing a biological active substance for the patient, and include a process of introducing the liposome capsule medication unit according to claim 1 into a subject.
[Claim 13]A method according to claim 12 by which oral introduction of said medication unit is carried out.
[Claim 14]A method according to claim 12 by which topical application of said medication unit is carried out.
[Claim 15]A method according to claim 12 by which said medication unit is introduced in an eye.
[Claim 16]A method according to claim 12 by which said medication unit is introduced in a nose.
[Claim 17]A method according to claim 12 by which said medication unit is introduced in a large intestine.
[Claim 18]A method according to claim 12 by which said medication unit is introduced in a vagina.

[Translation done.]